To: Dr. Genevieve Matanoski, Chair, EPA SAB Arsenic Review Panel
From: Kenneth Brown
Date: January 16, 2006
Subject: Comments on the EPA SAB Report Regarding Inorganic Arsenic

This memo summarizes my comments on the draft report of the EPA Science Advisory Board, Arsenic Review Panel (December 27, 2005). The comments focus on statistical modeling and interpretation of dose-response assessment of the S.W. Taiwan data plus an additional comment.

1. Linear vs nonlinear statistical model.

Recommendation: The EPA should seriously consider the model with the best statistical fit to the data (the quadratic model on p. 34) as the model of choice for dose-response assessment of the S.W. Taiwan data, not just recommend it to test sensitivity of the assumption of linearity.

Comments: The SAB report notes that EPA's 2005 guidelines are clear that linear extrapolation below the point of departure is the method to be used (p.33), but that does not mean that there is insufficient justification for the choice of a specific nonlinear form of the dose-response relationship (fit to the whole observed range), or that the final recommendation of NRC(2001) to base current risk assessments on a linear dose response model that includes the S.W. Taiwan population as a comparison group seems the most appropriate approach (p.34). The draft explicitly states that the NRC(2001) found the model that best fit the data, based on the Akaike Information Criterion (AIC) to be a nonlinear model (a model with hazard function quadratic in dose (p.33-34)). The guidelines do not recommend a linear dose-response curve as a default model fit to the entire range of observations when the mode(s) of action are unknown. Unless there is a biological basis to suggest otherwise, there is little basis for choosing a linear dose response model over the model that fits best statistically. The NRC (2001) recommendation to use a linear dose-response model is not well supported.

The discussion in NRC (2001) on the choice of model is worth reviewing. The executive summary notes that a model should be used that is biologically plausible and provides a reasonable statistical fit to the data, and that for the S.W. Taiwan data, that model is the Poisson model with linear dose (p.11). That conclusion appears contrary to the conclusions of Morales et al. (2000), to the visual evidence from the plots of Morales et al. (see Figure 1 attached) that are also reproduced in NRC (2001), and to explicit reservations in the body of the NRC (2001) report. For example: (1) A wide range of different models can be used to fit the arsenic data currently available, and no clear biological basis exists for distinguishing among them (p.151). (2) The mechanisms by which arsenic causes cancer are not well understood. It is unclear what the shape of the dose-response curve is at low doses, and whether the magnitude of exposure or duration of exposure is more important in cancer risk (p.160). (3) Several possible modes-of-action are discussed that are characterized by a sublinear, linear, or supralinear shape, depending on where the observed dose-range falls (p.119). The comment in the

executive summary supporting the Poisson model with linear dose is not warranted on either statistical or biological grounds, according to the internal text of the NRC report itself.

2. Analyzing the data from single-well villages.

Recommendation: Emphasis should be placed on what can be learned about the dose-response relationship from the subset of villages with a single well or a very narrow range (spread) of arsenic concentrations.

Comments: There is clearly high potential for exposure misclassification in villages with multiple wells. The SAB draft recommends doing a sensitivity analysis of those villages. More attention should also be given, however, to analyzing the data from single well villages alone. Of the 42 villages, there are 20 with single wells and another 3 wherein the spread (difference between lowest and highest well concentrations) is negligible (<25 μg/L), giving a total of 23 villages. Fitting a Poisson model to the data does not allow for a flat or decreasing slope in the low dose region, but that is what the data indicate when a flexible smoothing spline is used to fit the data using combined bladder/lung cancer mortality as the response. This is clearly illustrated in Figures 2a and 2b attached. The figures suggest a flat or decreasing response in the low dose region (<100 μg/L) and little increase in response overall, for males or females (the exposures run up to about 500 μg/L). This response from the S.W. Taiwan data is consistent with the lack of evidence of an effect reported in meta-analyses of low-dose studies.

3. Using southwestern Taiwan as an external comparison population.

Recommendation: An external comparison population such as southwestern Taiwan should not be used.

Comments: The SAB draft follows the NRC recommendation "to base current risk assessments on a linear dose response model that include the S.W. Taiwan population as a comparison group" (p.34). Figures 2a and 2b raise questions about the appropriateness of including the southwestern Taiwan region as a comparison population. The figures suggest that the study data, for all the curves shown, are most consistent with a background rate of bladder/lung cancer (i.e., not attributable to arsenic) much higher than the comparison population. This suggests that the comparison population and study population are different, and using a comparison population in the analysis would likely bias the outcome instead of adding stability and confidence in the low dose region. Additionally, if the background rate in the study population is higher than the southwestern region, and all of Taiwan as well, as the analysis of Morales et al. (2000) indicates, then one must question the validity of extrapolating low-dose risk estimates from the study population to either southwestern Taiwan, or to all of Taiwan, and even more so to the U.S. population.

4. An additional comment

(p.33) "…there have been a number of studies in different populations across different countries that seem to support a possible linear dose-response between exposure from drinking water and internal cancer risks (particularly in Taiwan, Chile and Argentina). However, the dose-response relationships are observed at higher exposure levels (> 100 ppb)."

This is speculative and should be rephrased or eliminated. Dose-response modeling has not been explored in these studies from Chile and Argentina to the extent of the S.W. Taiwan data to confirm a linear dose-response relationship. No detailed quantitative dose-response analysis of these studies appears in the NRC reports, Morales et al., or the EPA toxicological review.

Figure 1 Plots from Morales et al. (2000)

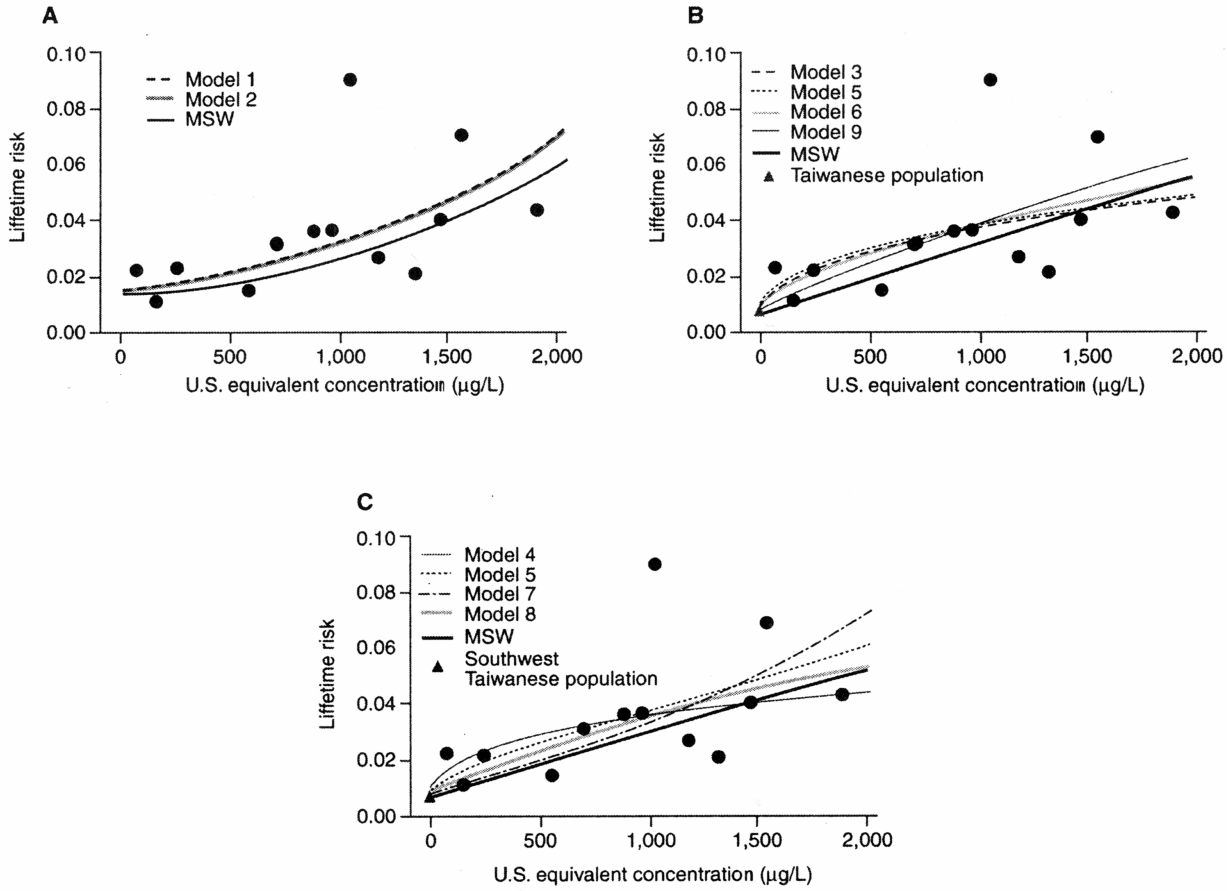

Figure 2a Male data fit by smoothing spline

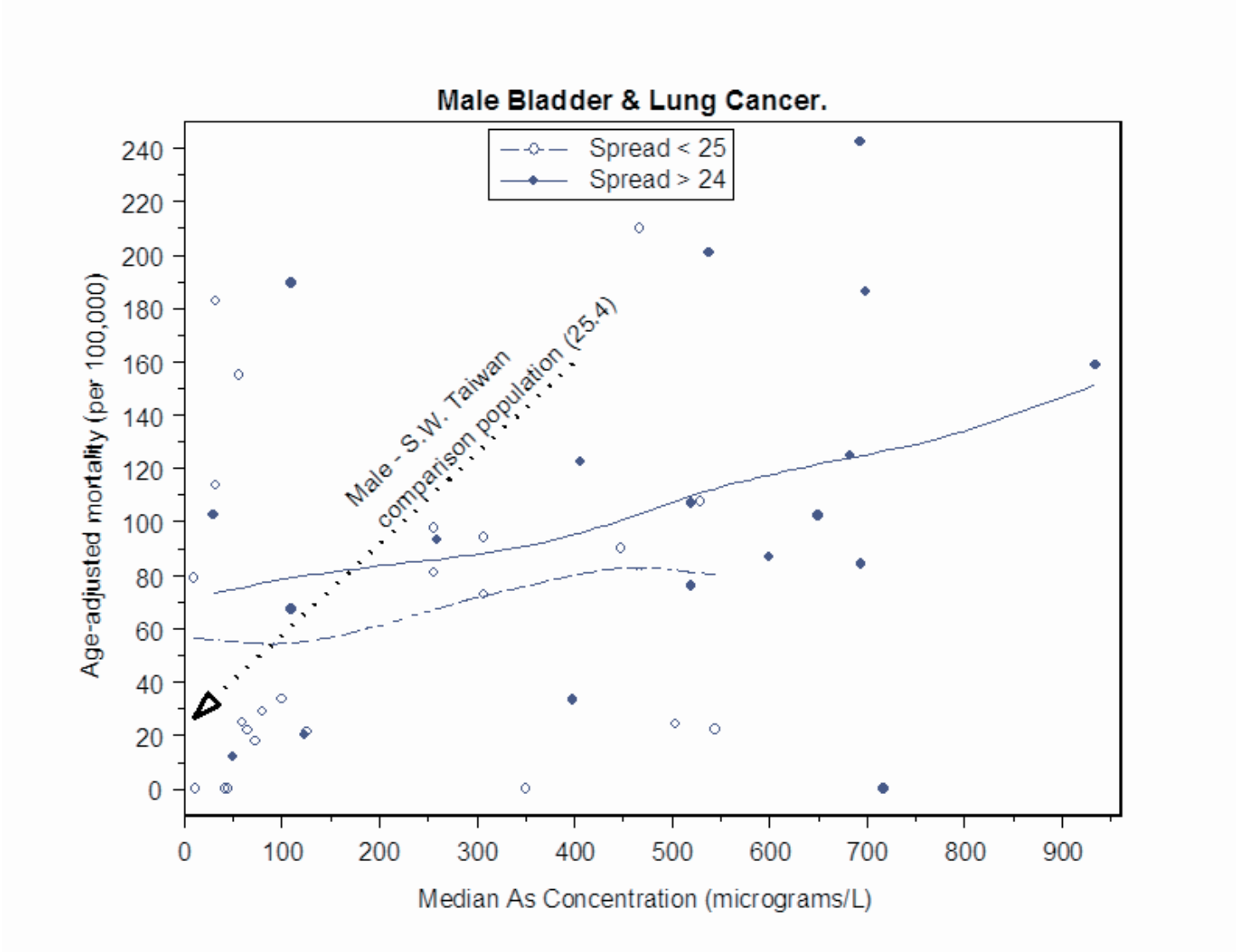

Figure 2b. Female data fit by smoothing spline